Researchers identify key signaling pathway involved in lymphoma tumor formation

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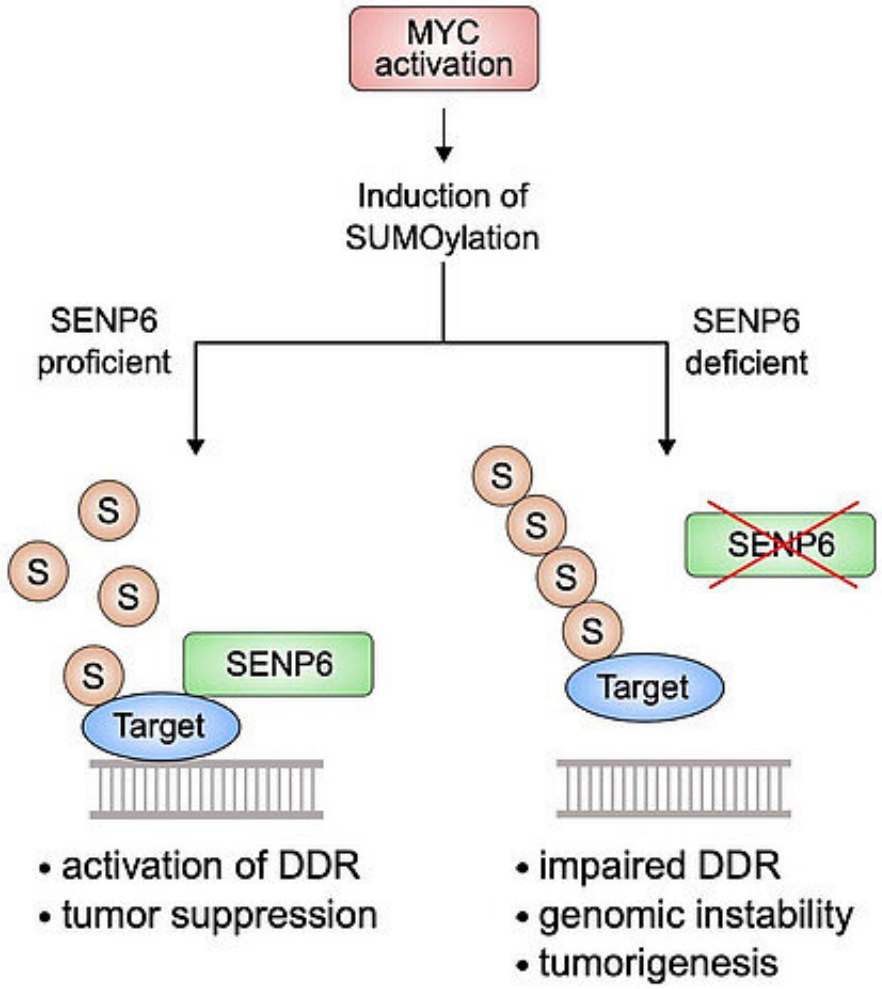

Cellular signaling pathways in carcinogenesis: SUMO modifications (S) of target proteins and DNA repair (DDR) in the presence and loss of SENP6. Credit: Charité | Markus Schick

There are myriad reasons why cancers develop. By studying genes which are altered in people with lymphoma, a multidisciplinary team of researchers, led by Charité – Universitätsmedizin Berlin and Goethe University Frankfurt, have identified a key mechanism involved in disease development. This signaling pathway, which the researchers describe in detail, controls the repair of DNA damage. Published in *Nature Communications*, these findings could open potential new avenues for treatment.

Cancer is associated with the disruption of various cellular signaling pathways. One of these pathways, 'SUMOylation', is responsible for the targeted modification of proteins, determining factors such as their lifespan and location within the cell. "As part of our study, we identified a previously unknown cancer gene, which controls this key cancer signaling pathway and could therefore offer a target for new cancer treatments," says Prof. Dr. Ulrich Keller, Head of the Department of Hematology, Oncology and Cancer Immunology on Charité's Campus Benjamin Franklin and Group Leader (Keller Lab) at the Max Delbrück Center for Molecular Medicine (MDC).

In an effort to identify and characterize these central control mechanisms, a team of researchers, led by Charité and Goethe University, systematically searched for genes which are found to be altered in lymphoma (cancer of the lymphatic system). Working with a mouse model, the researchers opted for a 'transposon system', a tool which utilizes mobile DNA segments (known as transposons or 'jumping genes') to randomly switch individual genes on and off in order to study their effects on tumor development. "Numerous large sequencing studies conducted over the past few years have produced detailed characterizations of cancer genomes, visualizing the complexity and heterogeneity of underlying modifications using 'molecular maps'. However, these abnormalities often only occur in small groups of patients, rendering any interpretation of their significance more

difficult," explains first author Dr. Markus Schick, Team Leader and Principal Investigator at Charité's Department of Hematology, Oncology and Cancer Immunology. He adds: "Our approach enabled us to identify many previously unknown cancer genes—among them the SENP6 gene, which is missing in approximately one third of all lymphoma patients. On the basis of this discovery, we then established the gene's mechanism of operation and developed a treatment strategy."

The gene's role in cancer pathology had not previously been understood. SENP6, the protein encoded by this gene, removes SUMO modifications from other proteins inside the cell. By doing so, it also controls the proteins' interactions with one another. The research team were able to prove that switching off SENP6 leads to cancer development, meaning it acts as a tumor suppressor. In healthy cells, SENP6 plays a key role in the repair of DNA damage. Loss of the gene results in this function being impaired. This leads to an accumulation of DNA damage which ultimately facilitates cancer development. In this study, however, the researchers were able to effectively suppress cancer growths following the loss of SENP6. They did so by inhibiting PARP, an enzyme involved in the repair of DNA damage, using drugs already licensed for breast cancer treatment. "Combining the biochemical expertise available at Frankfurt with the lymphoma and mouse genetics expertise at Charité in Berlin was key to the success of this project," emphasizes Prof. Dr. Stefan Müller, whose research group at Goethe University's Institute of Biochemistry II was involved in characterizing the SENP6 protein's function.

Summarizing the research, Prof. Keller says that their "findings enabled us to establish SENP6 as a biomarker for treatment success following PARP inhibitor therapy. We are currently investigating whether the mechanism described here might also be contributing to the development of cancers other than lymphoma." He says that "the aim of personalized medicine is to develop treatments which precisely match

the specific needs of the individual patient. The next step, therefore, will be to conduct clinical studies to test whether these inhibitors offer an innovative, targeted treatment option in cancers characterized by the loss of SENP6. There is also the option of using them as part of combination therapy regimens, which are still too rarely used but hold enormous potential, particularly when they are selected based on an individual patient's tumor biology."

More information: Markus Schick et al, Genetic alterations of the SUMO isopeptidase SENP6 drive lymphomagenesis and genetic instability in diffuse large B-cell lymphoma, *Nature Communications* (2022). DOI: 10.1038/s41467-021-27704-8

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